THE CONCEPT OF AUTOIMMUNE LIVER DISEASE*

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HISTORICAL BACKGROUND

THE first attribute of present-day chronic active hepatitis to be recognized was a raised level of gamma globulin in the blood, reported in 1941 in cases of cirrhosis of the liver by workers applying the moving boundary electrophoretic analysis of Tiselius to human sera.

Autoantibodies to liver were described in 1944 by Eaton, Murphy, and Hanford[1] in cases of acute hepatitis. These authors speculated that liver antibody, once produced, could combine with additional antigen in situ in the liver cells and cause further damage after the acute infectious process had subsided. This idea attracted some attention at the time, but in the early 1940s chronic hepatitis as a disease entity was not recognized clearly.

The history of what is now known as chronic active hepatitis recently has been reviewed.[2] The disease can be perceived in a description in 1947 by Himsworth,[3] and was receiving considerable attention in 1948 from Wood and his colleagues[4] at the Clinical Research Unit in Melbourne, where it was described as chronic nonsuppurative hepatitis. The predisposition of young females to the disease was emphasized by Waldenström[5] and Kunkel and his colleagues.[6] Saint and his colleagues[7] in Melbourne, in differentiating what they termed active and inactive chronic hepatitis, initiated an increasing tempo of interest in what they called active chronic hepatitis (chronic active hepatitis in American usage). It was recognized from clinical observations that chronic hepatitis played a substantial role in all cases of cirrhosis.

From 1951 to 1955 the concept of autoimmunity was developing.

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For example, in 1951 the adjectives "acquired" and "idiopathic" began to be replaced by the term "autoimmune" in describing the type of hemolytic anemia associated with a positive Coombs antiglobulin reaction.[8] The autoantibody nature of the lupus erythematosus (LE) cell-inducing factor was recognized in 1954 by Miescher,[9] and autoimmmunity became recognized in thyroid disease virtually simultaneously from studies in animals by Witebsky and his colleagues[10] and from studies in patients with Hashimoto's disease by Roitt, Doniach, and their colleagues.[11] Hence, the finding in 1955 in Melbourne by Joske and King[12] that chronic active hepatitis is associated with a positive LE cell test stimulated an interest in autoimmunity as a component of that disease. In fact, it was soon shown that particular cases of chronic hepatitis tended to give LE-cell reactions, and these were designated as lupoid hepatitis.[13] At the same time, in Melbourne Gajdusek was studying the complement-fixation reaction using human tissue extracts as antigen:[14] it was found that certain highly reactive sera could be derived from patients with chronic active hepatitis or primary biliary cirrhosis as well as from those with systemic lupus erythematosus (SLE) or Waldenström's macroglobulinemia.[15] These clinical observations contributed to the formulation by Burnet[16] in 1959 of his clonal selection theory of the production of antibody and his forbidden clone theory of autoimmunity.

Thus, by 1960 chronic active hepatitis (CAH) and primary biliary cirrhosis (PBC) were regarded as forbidden clone types of autoimmune diseases which resulted from immunopathic reactions in the liver; the evidence (admittedly circumstantial) was summarized in 1961 in the form of these markers of autoimmunity:[17] hypergammaglobulinemia (present in both CAH and PBC), autoantibodies to nuclei and (recognized later) to smooth muscle in CAH, and to tissue extracts (recognized later as mitochondrial) in PBC, lymphoid and plasma cell aggregates in the target organ (the liver), deposit of gamma globulin in tissues (recognized in the kidney in cases of CAH), associations of CAH with other known immunopathic diseases, and improvement in the disease effected by treatment with corticosteroid drugs (and, later, with immunosuppressive drugs).

In a discussion of the pathogenesis of chronic hepatitis which took place in 1961, I introduced the concept of continuing damage to the liver requiring a continuing cause.[17] The possibilities examined included

1) the persistence of an initial viral infection (this was discounted as unlikely since hepatitis B virus had not been discovered then), 2) vascular disorganization during regeneration causing ischemia (however, persistence of activity is observable well before nodulation and derangement of vasculature occurs), and 3) self-perpetuation resulting from autoimmunization. At that time it was not known whether the autoimmune reaction was a primary event or occurred as a supervening event after hepatitis.

In the mid-1960s various serological indications of autoimmunity, demonstrable by immunofluorescence, became recognized in CAH;[2] these included antinuclear autoantibody (presumably equivalent to the LE cell-inducing factor), smooth muscle autoantibody, and mitochondrial autoantibody. There was also recognition of the effectiveness of corticosteroids together with azathioprine in suppressing disease activity.[18] This, while not necessarily indicative of an autoimmune causation, at least pointed to the disease being caused more by the response of the host than by the direct activity of an intrahepatic pathogen.

The discovery, also in the mid-1950s, of the Au antigen[19] and its relation to infection with hepatitis B virus (HBV)[20] gave promise of fresh insight into the possibility of viral pathogenesis of chronic hepatitis. However, there proved to be wide differences in the number of carriers of the Au antigen (now known as HBAg) according to geographic area. Detailed studies in Australia indicated that chronic infection of the liver with HBV, as manifested by HBAg in the blood, was a most infrequent associate of chronic active hepatitis.[21] However, carrier rates of up to 66% of the cases described as chronic hepatitis were reported from other countries.[21] Also, in chronic hepatitis the evidence proved conflicting as to whether there was dissociation, association, or no relation between serological markers of autoimmunity and HBAg; many reports described complete dissociation or only slight overlap, whereas others claimed that autoantibodies were equally frequent in HBAg positive and HBAg negative chronic hepatitis.[2]

This historical survey can be completed by reference to the finding in our laboratory of an association between chronic active hepatitis (but not primary biliary cirrhosis) and the human histocompatibility antigen HL-A 1,8[22] which is known to be associated with various other immunopathic diseases.

FEATURES WHICH MAY DIFFERENTIATE THE SUBTYPES OF CHRONIC ACTIVE HEPATITIS (CAH) ASSOCIATED WITH AUTOIMMUNE MARKERS, HBAg IN SERUM, OR INDUCED BY DRUGS

Indices	*Autoimmune CAH*	*HBAg (Au) + vl CAH*	*Drug-induced CAH*
Age, sex	Mostly young, some old women	Mostly men	Middle-aged or old women
Race	Anglo-Saxon?	Southern European Asian	Unknown
Onset	¼ hepatitic ¾ insidious	Hepatitic, insidious, or latent	Usually hepatitic
Course	10 years?	Uncertain, variable	Recovery (if drug stopped)
Biopsy			
periportal necrosis	+++	+ or ±	++
plasma cells	+++	+	++
Cirrhosis	Almost always	Sometimes and hepatoma	If drug use is prolonged
γ globulin	↑↑↑	Normal or ↑	↑
Autoantibodies	+++	±	+
Treatment	Prednisolone azathioprine	Unknown	Withdraw drug
HL-A	1, 8	Same as controls	No data

Popular Questions on Autoimmunity in Disease (Including Liver Disease)

When the topic of autoimmune disease is introduced, several questions inevitably come up for discussion.

1) Can autoimmunity be implicated as a direct cause of any human disease and if so what diseases would qualify? The classical types of Coombs positive hemolytic anemia and immunopathic thrombocytopenic purpura are believed by most experts to be the direct result of the formation of autoantibody which attaches to the cell membrane and, with the participation of complement, effects cell lysis. There is an almost complete acceptance that autoimmunity is the cause of diseases comprising the "thyroid-gastric" cluster,[23] Hashimoto's thyroiditis, pernicious anemia-type gastritis, Addison's adrenal disease, and others. There is agreement that immune complexes are an important cause of the damage to tissue found in SLE and that autoantigens participate in the formation of such complexes. Some authors also consider various other diseases as autoimmune, including myasthenia gravis, pem-

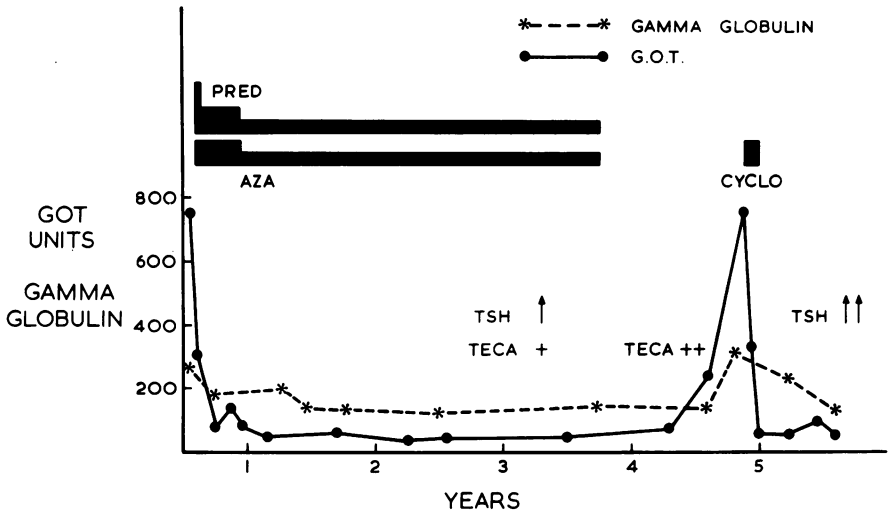
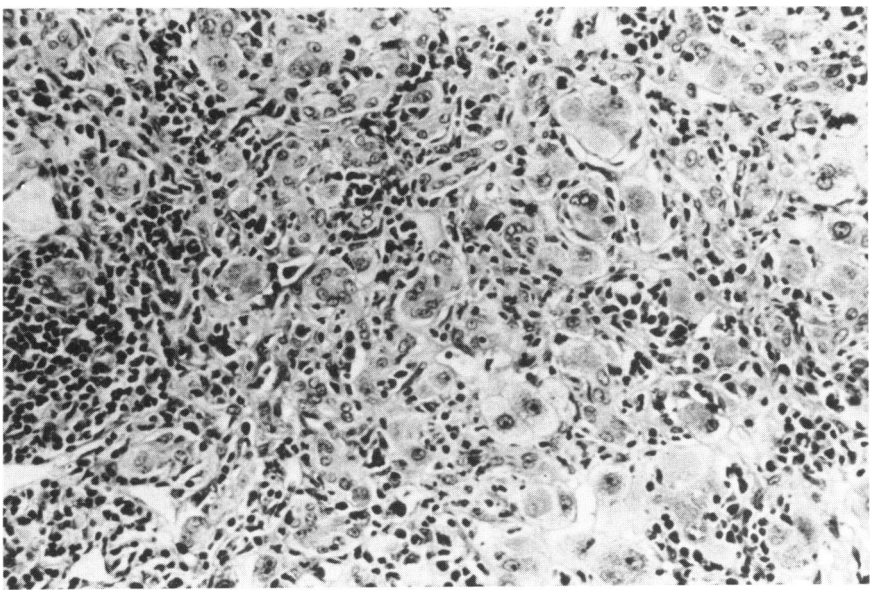


Fig. 1*a*. Time course of chronic active hepatitis (CAH) in patient M.C. showing response of serum glutamic oxalacetic transaminase (GOT) and gamma globulin (mg./10 ml.) to treatment with prednisolone (PRED), azathioprine (AZA), and (later) cyclophosphamide (CYCLO). Serial studies on sera showed that three years after the onset of hepatitis the level of thyroid-stimulating hormone (TSH) began to increase and the test for thyroid epithelial cell antibody (TECA) became positive.

phigus vulgaris, Sjögren's disease, and Goodpasture's disease of the lung and kidney on the basis of the close resemblance of the features of these diseases to those of accepted autoimmune pathogenesis.

In considering chronic active hepatitis, account must be taken of three known associations with this disease complex: 1) autoimmune serologic markers, 2) the carrier state for HBAg, and 3) allergic hepatitic reactions to certain drugs. This opens two pathways for theoretical discussion. One possibility is to treat the entire syndrome as one entity (chronic active liver disease),[24] accepting that, for the present, essential data for understanding it are lacking. The other possibility is to split chronic active hepatitis into subtypes characterized by autoimmune reactions, HBAg in serum, or adverse reaction to drugs, e.g., oxyphenisatin and alpha methyldopa. Each subtype then is believed to be caused by an immunopathic reaction to either an autoantigen or a neoantigen (virus or drug) in the liver. Possible differences in these subtypes are shown in the accompanying table.

2) What criteria allow diseases to be specified as autoimmune? The



Fib. 1*b*. Liver biopsy from patient M.C. at onset of hepatitis showing inflammatory septa, periportal necrosis, and lymphoid infiltrate characteristic of chronic active hepatitis.

main criterion is the demonstration of a target-specific autoantibody directed to a relevant, accessible, and vulnerable autoantigen. In certain diseases such autoantibody appears clearly pathogenic, as judged by *in vitro* observations, by the presence of fetal damage after transplacental passage or by both. A further criterion is the inducibility of a model disease by appropriate immunization of animals with the target antigen. In the case of the putative autoimmune liver diseases CAH and PBC, the evidence is not decisive. In favor of this classification is the relapsing course, histological features, clustering of the serologically demonstrable autoantibodies, and response to corticosteroid drugs in these diseases. However, there are two unresolved inconsistencies in the autoimmune concept: 1) the absence of humoral autoimmune reactivity to a liver-specific autoantigen, although there is demonstrable cell-mediated immunity using a liver-specific lipoprotein as the antigen[25] and 2) the general failure, with one exception,[26] to induce a model disease in animals by any form of immunization with liver extract. Considerable weight has been given in this unit to the existence of putative autoim-

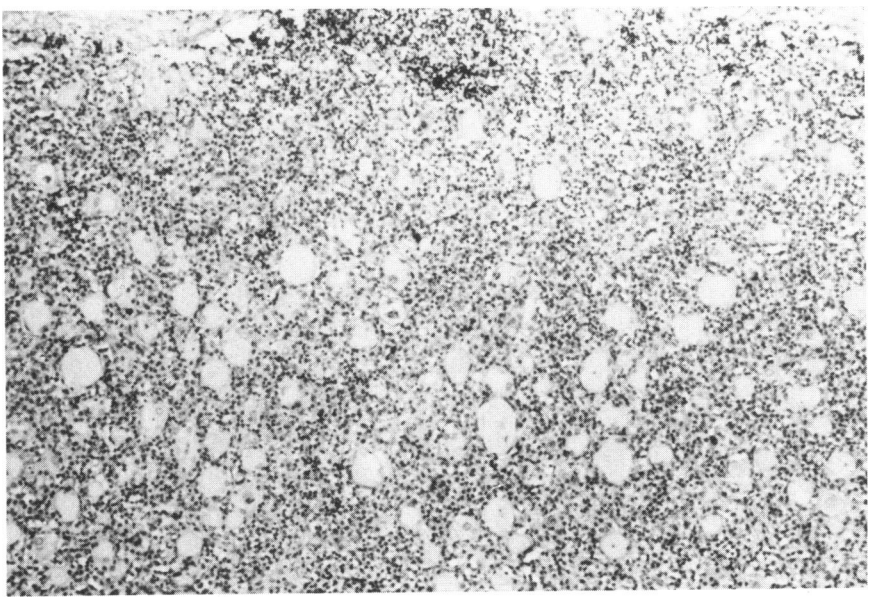


Fig. 1*c*. Biopsy of thyroid isthmus from patient M.C. after onset of myxedema showing acinar disruption and lymphoid infiltrate characteristic of Hashimoto's disease.

mune disorders in one patient and the relatives. Chronic active hepatitis coexists with various suspected autoimmune diseases,[17, 27, 28] as illustrated by the following case record (Figure 1*a*).

A 70-year-old woman (M.C.) was referred to a surgical department in 1967 with a four-week history of gradual painless jaundice with no antecedent history of injections, transfusions, contact with hepatitis, or exposure to potentially hepatotoxic drugs. Hepatic tumor was suspected, but laparotomy was performed and no tumor was found; a surgical biopsy of the liver (Figure 1*b*) revealed changes of chronic active hepatitis. There was elevation of serum levels of bilirubin (7.3 mg./100 ml.), oxalacetic glutamic transaminase (300 to 350 I.U.), and serum gamma globulin (5.3 g./100 ml.), a low level of serum albumin (1 to 2 g./100 ml.), increased retention of a standard intravenous dose of Bromsulphalein (37%, 45 minutes), strongly positive tests for LE cells, antinuclear antibody, and smooth-muscle antibody and negative tests for mitochondrial antibody, thyroid epithelial-cell antibody, and parietal-cell antibody. Treatment with prednisolone (10 mg. daily) and

azathioprine (100 mg. daily) induced full remission. These drugs were stopped in 1970 after three years of treatment. One year later, in 1971, there was a relapse which subsided after a short course of cyclophosphamide. The patient presented in May 1972 with clinically evident myxedema; the serum thyroxine level was 0.1 mg./100 ml. A surgical biopsy of the thyroid isthmus showed changes indicative of Hashimoto's thyroiditis with destruction of the gland (Figure 1*c*). Examination of stored serum samples allowed accurate dating of the onset of thyroiditis; in 1971 there was concurrent conversion to positivity of tests for antibodies to thyroid epithelial cells and colloid and the onset of a rise in the level of thyroid-stimulating hormone of the pituitary gland. Interestingly, this onset of autoimmune thyroiditis occurred during immunosuppressive treatment of chronic active hepatitis.

3) How is damage effected in autoimmune disorders? This question usually is answered by reference to the Coombs and Gell classification of Types I to IV of hypersensitivity reactions: anaphylactic, humoral cytotoxicity, immune complexes, and cell-mediated attack—to which are now added Type V, stimulating (membrane-reactive) autoantibody, and Type VI, cell-mediated cytotoxicity which is dependent on antibody (K cells).[29] In regard to the damage of chronic active hepatitis, none of these modes of immunopathic injury can be implicated: there is no liver-specific cytotoxic antibody, deposition in the liver of immune complexes, nor evidence for activity of cytotoxic T cells. By analogy with damage in other autoimmune processes, notably Hashimoto's disease,[29] cytotoxicity by K cells could be invoked; the antibody component could be the smooth-muscle antibody with its known reactivity with contractile material of the cell surface. This question awaits experimental investigation.

4) How are autoimmune states created? The lesion of autoimmunity has been the subject of innumerable discussions and speculations; the likelihood is that this lesion has a number of predisposing factors and is the end result of breakdown of several so-called fail-safe mechanisms. Current speculations include the following:

a) Forbidden clones. This theory[30] holds that the "lesion of autoimmunity" essentially is based on random somatic mutation among B or T lymphocytes which results in the appearance of immunocytes carrying receptors for self-antigens of such a character that contact with antigen causes an ongoing immune response rather than tolerance.

This model is attractive as a theory but does not readily open up experimental avenues.

b) Cross-reactivity. Antigenic determinants are displayed on micro-organisms or drugs with similarities to self-antigens; these supposedly would trigger clones of lymphocytes capable of reacting with the corresponding autoantigen, thus initiating an autoimmune response and the possibility of disease.

c) Viral infection. This is repeatedly invoked as a basis for states of autoimmunity; it could act by a) causing damage and releasing autoantigen, b) presenting determinants which are cross-reactive with self (see 2 above), or c) infecting lymphoid tissue and so initiating aberrant clones of lymphocytes. Alternatively, d), a virus may be maintained as a persistent tolerated infection in liver cells (e.g., hepatitis B virus) and cause expression of immunogenic nonself-determinants on the cell surface; this concept has been presented over many years in various forms, e.g., the self + x concept of Lawrence.[31] Chronic active hepatitis is similar to diseases in animals which have a "virus-cum-immunopathy" type of pathogenesis, for example, Aleutian disease of minks.[32] Candidate viruses for such a role in chronic active hepatitis include HBV (but HBAg is demonstrable only in a small minority of Australian cases of chronic active hepatitis[21]) and hepatitis A virus, for which we still await application of recently developed techniques for identification of infection.

d) Drug allergy. Drugs are known to be concerned in the induction of autoimmune states, including lupus syndromes (procainamide, hydralazine) and autoimmune hemolytic anemia (alpha methyldopa).[33] In so-called drug-induced chronic active hepatitis there are two possibilities to consider: either the drug is bound to structural proteins of the liver and creates a "neoantigen" or the drug in some unknown way permits the expression of autoimmunity, as exemplified by chronic hepatitis induced by oxyphenisation.[34] Drug-induction is an interesting theory, but it does not appear applicable to the prototype form of chronic active hepatitis as seen in young Caucasian females.

e) Failure of suppressor T cells. In experimental systems a class of T cells has been described which inhibits rather than helps immune responses.[35] The concept has been developed that such suppressor T cells somehow control self-reative B cells and that the dysfunction of suppressor cells could allow the escape of autoreactive B cells, cul-

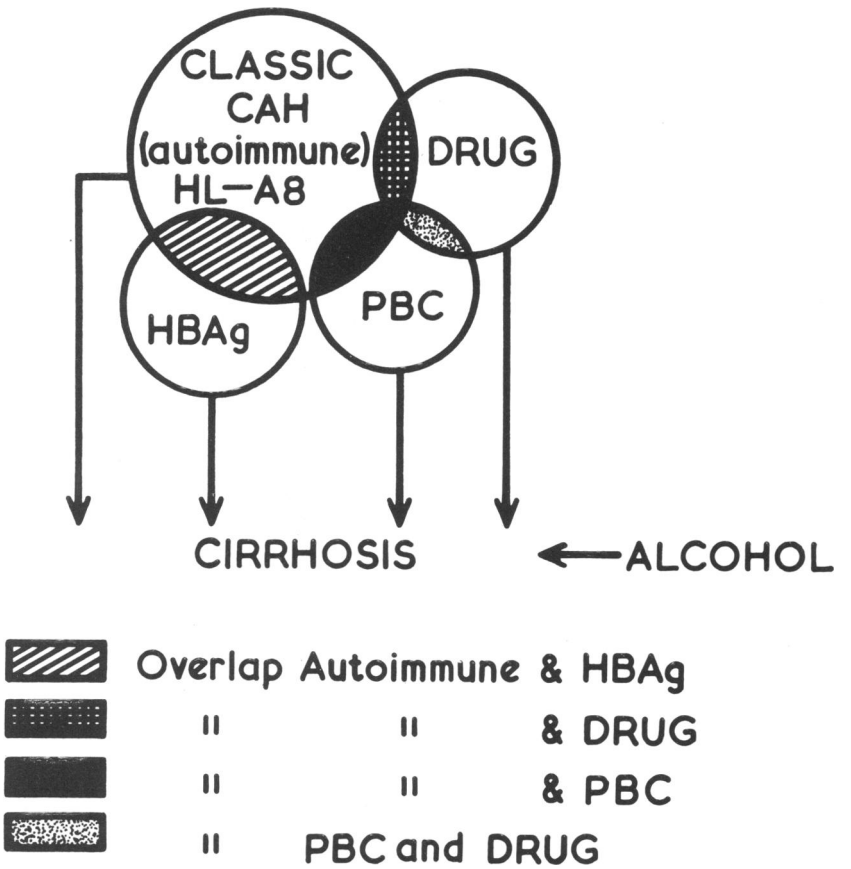


Fig. 2. Diagrammatic illustration of the concept of subsets of chronic liver disease which have some degree of overlap of attributes and the tendency for progression to cirrhosis. CAH = chronic active hepatitis, PBC = primary biliary cirrhosis.

minating in autoimmune disease.[36] Favoring this concept to some degree is the evidence for hyporeactivity in tests of T-cell function in various autoimmune diseases,[37] including chronic active hepatitis and primary biliary cirrhosis. However, as yet there is no formal demonstration of an effect of suppressor T cells in man.

f) Genetics and autoimmune responses. It is to be expected from data in the field of experimental immunogenetics[38] that in man there would be some genetic influence over responses to autoantigens and, thus, secondarily on the occurrence of autoimmune disease. The latter possibility has been approached by studies on family members related

to prospositi with autoimmune disease and by examining associations of given diseases with histocompatibility antigens, the expression of which is linked in mice to immune responses to particular antigenic determinants. These approaches have yielded a curious discrepancy in results, in that well-defined autoimmune diseases with strong associations within families (autoimmune thyroiditis, pernicious anemia)[39] give little hint of specific HL-A associations.[40] On the other hand, less well-defined immunopathic diseases with relatively weak familial clustering (ankylosing spondylitis, gluten enteropathy) show strong HL-A associations (W27 and HL-A8, respectively). Chronic active hepatitis (HL-A8) is a further case in point. Some familial association does exist,[41] but this is exceptional; yet the association with HL-A8 is strong, according to studies in Melbourne,[22] Germany,[42] and London.[43] The impression is gained that cases of chronic active hepatitis which are HL-A8 negative could show differing attributes from the classical or prototype cases which are HL-A8 positive. Unfortunately, it has not yet been ascertained how histocompatibility antigens on the lymphocyte surface dictate patterns of responsiveness which become expressed as disease—this holds particularly for chronic active hepatitis.

Conclusions

Chronic active hepatitis has become recognized over the past 20 years as a disease process characterized by: 1) a relapsing course, 2) progressive inflammatory destruction of liver cells, culminating in cirrhosis, 3) autoimmune serological reactions, and 4) responsiveness to corticosteroid drugs. I believe that there are subsets of chronic immunopathic diseases of the liver, as depicted in Figure 2, with degrees of overlap and a common tendency to progress to cirrhosis. The immunopathic stimuli appear to differ among the subsets. The classic type, earlier described as lupoid hepatitis, is a candidate autoimmune disease. However, the immunogen responsible for initiating the disease and the antigenic target of the immune attack are still to be identified.

REFERENCES

1. Eaton, M. D., Murphy, W. D., and Hanford, V. L.: Heterogenetic antibodies in acute hepatitis. *J. Exp. Med.* 79:539, 1944.
2. Mackay, I. R.: Chronic Active Hepatitis. In: *Frontiers of Gastrointestinal Research. I. Immune Disorders of the Digestive System.* Basel, Karger, 1975, pp. 142-87.
3. Himsworth, H. P.: *The Liver and its*

Diseases. Oxford, Blackwell, 1947.
4. Wood, I. J., King, W. E., Parsons, P. J., Perry, J. W., Freeman, M., and Limbrick, L.: Non-suppurative hepatitis: A study of acute and chronic forms with special reference to biochemical and histological changes. *Med. J. Aust. 1*:249, 1948.
5. Waldenström, J.: Leber, Blutproteine und Nahrungseiweiss. *Tag. Stoffwechselkr.* (Suppl.) *15*:8, 1950.
6. Kunkel, H. G., Ahrens, E. H., Eisenmenger, W. J., Bongiovanni, A. M., and Slater, R. J.: Extreme hypergammaglobulinemia in young women with liver disease. *J. Clin. Invest. 30*:654, 1951.
7. Saint, E. G., King., W. E., Joske, R. A., and Finckh, E. S.: The course of infectious hepatitis with special reference to prognosis and the chronic stage. *Aust. Ann. Med. 2*:113, 1953.
8. Young, L. E., Miller, G., and Christian, R. M.: Clinical and laboratory observations on autoimmune hemolytic disease. *Ann. Intern. Med. 35*:507, 1951.
9. Miescher, P. and Fauconnet, M.: L'absorption du facteur L.E. par des noyaux cellulaires. *Experientia 10*:252, 1954.
10. Witebsky, E., Rose, N. R., Terplan, K., Paine, J. R., and Egan, R. W.: Chronic thyroiditis and autoimmunization. *J.A.M.A. 164*:1439, 1957.
11. Roitt, I. M., Doniach, D., Campbell, P. N., and Hudson, R. V.: Autoantibodies in Hashimoto's disease (lymphadenoid goitre). *Lancet 2*:820, 1956.
12. Joske, R. A. and King, W. E.: The L.E. cell phenomenon in active chronic viral hepatitis. *Lancet 2*:477, 1955.
13. Mackay, I. R., Taft, L. I., and Cowling, D. C.: Lupoid hepatitis. *Lancet 2*:1323, 1956.
14. Gajdusek, D. C.: An "autoimmune" reaction against human tissue antigens in certain acute and chronic diseases: I: Serological investigations. *Arch. Intern. Med. 101*:9, 1958.
15. Mackay, I. R. and Gajdusek, D. C.: An "autoimmune" reaction against human tissue antigens in certain acute and chronic diseases. II. Clinical correlations. *Arch. Intern. Med. 101*:30, 1958.
16. Burnet, F. M.: *The Clonal Selection Theory of Acquired Immunity.* Cambridge, Cambridge University Press, 1959.
17. Mackay, I. R.: The problem of persisting destructive disease of the liver. *Gastroenterology 40*:617, 1961.
18. Mackay, I. R.: Immunosuppressive drugs and chronic hepatitis. *Med. J. Aust. 1*:1207, 1972.
19. Blumberg, B. S., Gerstley, D. A., Hungerford, D. A., London, W. T., and Sutnick, A. T.: A serum antigen (Australia antigen) in Down's syndrome, leukemia and hepatitis. *Ann. Intern. Med. 66*:924, 1967.
20. Prince, A. M.: An antigen detected in the blood during the incubation period of serum hepatitis. *Proc. Nat. Acad. Sci. U.S.A. 60*:814, 1968.
21. Cooksley, W. G. E., Powell, L. W., Mistilis, S. P., Olsen, G., Mathews, J. D., and Mackay, I. R.: Australia antigen in active chronic hepatitis in Australia: Results in 130 patients from three centres. *Aust. N.Z. J. Med. 2*:261, 1972.
22. Mackay, I. R. and Morris, P. J.: Association of autoimmune active chronic hepatitis with HL-A 1, 8. *Lancet 2*:793, 1972.
23. Mackay, I. R.: Autoimmune disease. *Med. J. Austr. 1*:696, 1969.
24. Summerskill, W. H. J.: Chronic inflammatory liver disease reexamined: Prognosis hopeful. *Gastroenterology 66*:450, 1974.
25. Miller, J., Smith, M. G. M., Mitchell, C. G., Reed, W. D., Eddleston, A. L. W. F., and Williams, R.: Cell-mediated immunity to a human liver-specific antigen in patients with active chronic hepatitis and primary biliary cirrhosis. *Lancet 2*:296, 1972.
26. Meyer zum Büschenfelde, K. H., Kossling, F. K., and Miescher, P. A.: Experimental chronic active hepatitis in rabbits following immunization with human liver proteins. *Clin. Exp. Immun. 11*:99, 1972.
27. Read, A. E., Sherlock, S., and Harrison, C. V.: Active "juvenile" cirrhosis as part of a systemic disease and the effect of corticosteroid therapy. *Gut :4*

378, 1963.

28. Golding, P. L., Smith, M., and Williams, R.: Multisystem involvement in chronic liver disease. Studies on the incidence anl pathogenesis. *Amer. J. Med. 55*:772, 1973.
29. Irvine, J.: Autoimmunity in endocrine disease. *Proc. Roy. Soc. Med. 67*:548, 1974.
30. Burnet, F. M.: *Autoimmunity and Autoimmune Disease.* Lancaster, Medical and Technical Publ., 1972.
31. Lawrence, H. S.: Homograft sensitivity: An expression of the immunologic origins and consequences of individuality. *Psysiol. Rev. 39*:811, 1959.
32. Henson, J. B. and Gorham, J. R.: Animal model: Aleutian disease of mink. *Amer. J. Path. 71*:345, 1973.
33. Whittingham, S., Mackay, I. R., Whitworth, J. A., and Sloman, J. G.: Antinuclear antibody response to procainamide in man and laboratory animals. *Amer. Heart J. 84*:228, 1972.
34. Reynolds, T. B., Peters, R. L., and Yamada, S.: Chronic active and lupoid hepatitis caused by a laxative, oxyphenisatin. *New Eng. J. Med. 280*:813, 1971.
35. Gershon, R. K.: T cell control of antibody production. *Contemp. Topics Immunobiol. 3*:1, 1974.
36. Allison, A. C., Denman, A. M., and Barnes, R. D.: Cooperative and controlling functions of thymus-derived lymphocytes in relation to autoimmunity. *Lancet 2*:135, 1971.
37. Toh, B. H., Roberts-Thomson, I. C., Mathews, J. D., Whitingham, S., and Mackay. I. R.: Depression of cell-mediated immunity in old age and the immunopathic diseases, lupus erythematosus, chronic hepatitis and rheumatoid arthritis. *Clin. Exp. Immunol. 14*: 193, 1973.
38. Benacerraf, B. and McDevitt, H. O.: Histocompatibility-linked immune response genes. *Science 175*:273, 1972.
39. Doniach, D., Roitt, I. M., and Taylor, K. B.: Autoimmunity in pernicious anaemia and thyroiditis. A family study. *Ann. N.Y. Acad. Sci. 124*:605, 1965.
40. Whittingham, S., Youngchaiyud, U., Mackay, I. R., Buckley, J. D., and Morris, P. J.: Thyrogastric autoimmune disease: Studies on the cell-mediated immune system and histocompatibility antigens. *Clin. Exp. Immunol. 19*:289, 1975.
41. Galbraith, R. M., Smith, M., Mackenzie, R. M., Tee, D. E., Doniach, D., and Williams, R.: High prevalence of seroimmunologic abnormalities in relatives of patients with active chronic hepatitis or primary biliary cirrhosis. *New Eng. J. Med. 290*:63, 1974.
42. Freudenberg, J., Erdmann, K., Meyer zum Büschenfelde, K. H., Förster, E., and Berger, J.: HL-A bei Lebererkrankungen. *Klin. Wschr. 51*:1075, 1973.
43. Galbraith, R. M., Eddleston, A. L. W. F., Smith, M. G. M., Williams, R., MacSween, R. N. M., Watkinson, G., Dick, H., Kennedy, L. A., and Batchelor, J. R.: Histocompatibility antigens in active chronic hepatitis and primary biliary cirrhosis. *Brit. Med. J. 3*:604, 1974.